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Purified Mineral-Free Water for Pharmaceutical Purposes*

By J. W. E. Harrisson†, R. J. Myers‡ and D. S. Herr‡

Most pharmaceutical processes require a water equal in quality to that produced by distillation. This is known to every large-scale pharmaceutical manufacturer and is further evidenced by Pharmacopœial requirements. The U. S. P. XII officially recognizes water of natural origin, and three categories of mechanically produced water, namely, distilled water, sterilized distilled water and injection water, the latter being distilled water prepared under specific requirements.

Of the 179 galenicals of the Pharmacopœia which embrace dilute acids to unguents, water is a constituent part of 116. In 91 of these, distilled water is required which includes 14 official injections, 6 use natural waters and 19 for no explainable reason, except convenience, employ both natural and distilled water. Greater understanding is necessary to establish why Tincture of Colchicum Seed is prepared with distilled water, although for Tincture of Belladonna and most other tinctures natural water is directed to be used.

The importance of a mineral-free water in maintaining product stability is well recognized. Clarity, color, taste and sometimes actual physiological activity are influenced by the composition of the water employed. The blandness of the much-used household remedy Milk of Magnesia is related closely to the quality of water employed in its manufacture. Clarity and stability of "Magnesium Citrate Solution," which is now produced in a large-scale manufacturing process, is enhanced by use of water meeting distilled water specifications. "Silk-free" liniment can only be produced when either distilled water or mechanically softened water is used in their preparation.

The unsuitability of natural water in general for pharmaceutical purposes is evidenced by their wide divergence in composition. New York City has one water supply containing less than 30 p. p. m. of total solids, and two other supplies, one of which contains nearly 150 p. p. m. Philadelphia likewise has a duplicate system of water sources, each of which varies considerably in its composition; Indianapolis water contains nearly 400 p. p. m. of total solids, and many supplies in the central,

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southwestern and Gulf Coast states run as high as 1400 to 2000 p. p. m. of solids.

The Pharmacopœia attempts to permit the use of these waters in certain processes by defining a permissible natural water. In so doing it limits the amount of dissolved solids to 500 p. p. m., and requires that the *p*H in such water shall fall between 5.6 and 8.3.

Though in many sections of the country the common water supply might be sufficiently pure for many processes, or at least not contain serious impurities, in other sections the water would be totally unfit for use. The various salts in solution or suspension in ordinary water would often seriously interfere with the purity of many chemical substances whereas the purity of distilled water or water meeting distilled water requirements is beyond question and its use, therefore, removes all doubts.

Plant operations demand large volumes of water having distilled water characteristics, and even an establishment of moderate capacity needs daily hundreds of gallons of water of this quality. Equipment to produce such water and the attention necessary to keep such equipment scale-free are a costly factor in many operations. Until recently the only means of obtaining such water was by actual distillation. However, the discovery of ion-exchange resins by Adams and Holmes in 1935 (1) has resulted in the development, both in Europe and in the United States, of a process which makes possible for the first time the removal of all dissolved salts from natural waters without resort to distillation.

The term "synthetic resins" is commonly associated with industrial polymers, such as Bakelite, Plexiglas and Nylon or cellophane and plastic finishes on automobiles, books, textiles and metals. Hitherto, the practical utility of plastic and synthetic resins has been based primarily upon physical properties of the material. Thus, hardness, elasticity, lightfastness, solubility in certain solvents and viscosity have been the criteria upon which a decision as to the worth of a particular product was based. However, in 1935, Adams and Holmes announced in England that polyhydric phenol-formaldehyde resins, when polymerized to the insoluble "C" stage, would exhibit the phenomenon known as "base-exchange" and hence possess practical utility which is based primarily upon chemical properties.

In order to appreciate the significance of the statement that "a synthetic resin will undergo base-exchange," a few words of explanation are in order concerning base-exchange phenomena. It is to be recalled that the sodium alumino-silicates, known as greensands when occurring naturally and as synthetic gel zeolites when prepared commercially, are insoluble, more or less porous structures which contain loosely bound sodium ions which exchange with other cations when placed in contact with inorganic salt solutions. The exchange of sodium for calcium is stoichiometric and forms the basis for the removal of hardness from water supplies. The reaction is governed by the law of mass action and may be reversed by the use of an excess of sodium chloride, and this is the basis of the regeneration of the zeolite beds employed in commercial practice. Since the reaction is reversible, equilibria are established and the regeneration is never effected with a high degree of chemical efficiency. Practically all cations are exchanged by the sodium alumino-silicate, although the exchange for hydrogen and certain large ions imposes mechanical strain on the crystal structure (lattice) which gradually leads to disruption of the zeolite. Likewise, in solutions of high *p*H, or of low silica content, silica is lost from the zeolite structure and gradual disintegration follows. In spite of these shortcomings, however, greensands and gel zeolites have been and are still used today in a great number of installations where they are regenerated with salt, and are spoken of as operating in the "sodium cycle."

While the sodium cycle affords an opportunity to remove hardness-producing cations from solution, on the basis of chemical equivalencies the use of a sodium exchanger must involve the substitution of two sodium ions for each calcium or

magnesium ion and result in an increase of total solids. To afford an opportunity to exchange all cations by hydrogen ions, the so-called "carbonaceous zeolites" were developed about 1930. The hydrogens of the sulfonic acid groups in the carbonaceous zeolites generally prepared by the sulfonation and oxidation of complex organic

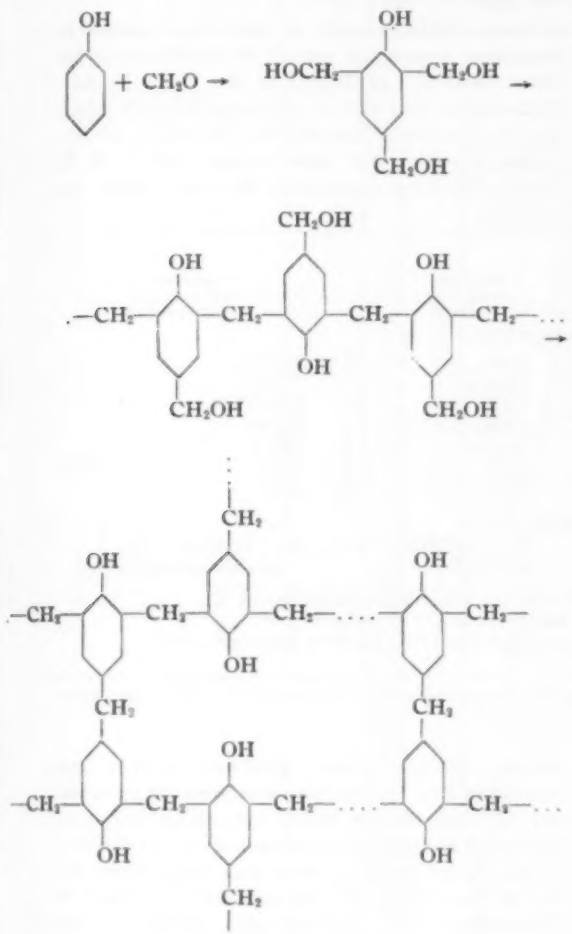


Fig. 1.

materials, such as coal, wood, lignite, etc., similar to the sodium atoms in a zeolite, are exchangeable and, in fact, will exchange with all cations. The exchange of hydrogen for all cations leads to a reduction of total solids as well as a removal of hardness, and temporary hardness is converted to carbonic acid. Regeneration is effected by treatment of the exhausted exchanger by means of hydrochloric or sulfuric acid, and the exchanger is spoken of as operating in the "hydrogen cycle." Carbonaceous exchangers have been developed rapidly and are employed in a variety of ways in water purification.

Consideration of the physical structure of these exchangers shows that they are essentially large insoluble molecules which contain certain active groups available for ion-exchange. In the condensation of phenol with formaldehyde a large insoluble molecule is formed in which certain hydrogen atoms, those of the phenolic groups, are not involved in the condensation (see Fig. 1). The phenolic hydrogen is acidic in nature and Adams and Holmes postulated that an insoluble structure of this character would exhibit exchange of hydrogen atoms. The soundness of this concept has been established: the passage of a solution of an inorganic salt down through a column of particles of the resin polymerized to the insoluble stage produces an effluent in which the cations have been replaced by hydrogen, and the salts appear as the corresponding mineral acids. Regeneration of the "exhausted" resin with acid is readily effected, and repeated cyclic operation is possible.

Adams and Holmes also reasoned that an amine-formaldehyde resin would show removal of acids in consequence of the basic groups present in the polymerized resin. The polymerized amine-HCHO resin is used to remove hydrochloric and sulfuric acids from solutions, and the resin may be regenerated with alkaline solutions.

The discovery of Adams and Holmes opened the door to incalculable opportunities since these ion-exchangers may not only be used in all applications which hitherto employed siliceous and carbonaceous exchangers, but in addition offered advantages of a tailor-made product so that modifications could be made with unique properties such as very high efficiencies and high capacity, for particular applications.

For the first time, it is possible to remove all the salts from aqueous solutions, by passage of natural water through a double system of a hydrogen exchanger and an acid absorbent resin. The reactions of these products, as used in softening water

or for removal of salts from aqueous media, are illustrated by the following equations.

As with other chemical equilibria, the reactions are governed by the Law of Mass Action and the equilibria may be reversed by the use of higher concentrations of the products. This is the principle involved in the regeneration of the exhausted exchanger. The hydrogen-exchange resin may be regenerated with strong acid or salt solution, depending upon the cycle used, while the anion-exchange resin (which removes the acids as whole molecules) is regenerated with an alkaline solution, such as sodium carbonate.

	Resin Exchanger before Reaction		Salt in Water Being Treated		Insoluble Resin Salt Formed		Compound Remaining in Treated Water	
			Cation-Exchange Resin					
Sodium Cycle	$2NaR$	+	$CaSO_4$	=	CaR_2	+	Na_2SO_4	
	$2NaR$	+	$MgCl_2$	=	MgR_2	+	$2NaCl$	
	$2NaR$	+	$Ca(HCO_3)_2$	=	CaR_2	+	$2NaHCO_3$	
Hydrogen Cycle	$2HR$	+	$CaSO_4$	=	CaR_2	+	H_2SO_4	
	$2HR$	+	$MgCl_2$	=	MgR_2	+	$2HCl$	
	$2HR$	+	$Ca(HCO_3)_2$	=	CaR_2	+	H_2O	CO_2
	HR	+	$NaCl$	=	NaR	+	HCl	
			Anion-Exchange Resin					
Acid Removal	RX	+	H_2SO_4	=	$(RX)\cdot H_2SO_4$	−	No residual dissolved substances	
	RX	+	HCl	=	$RX\cdot HCl$			

RX = Anion-exchange resin such as Amberlite IR-4[a] with the acid binding substituent X.
NaR = Sodium salt of cation-exchange resin, such as Amberlite IR-1[a] in sodium cycle.
HR = Hydrogen derivative of cation-exchange resin, such as Amberlite IR-1[a] in hydrogen cycle.

[a] The Amberlite IR-resins are synthetic resin ion-exchange absorbents manufactured by The Resinous Products and Chemical Co., Philadelphia, Pa.

The technical details of operation are very numerous and have been examined in detail (2, 3, 4, 5). By the combination of a hydrogen-exchanger and an anion-exchanger it is possible to obtain "deionized water" which compares favorably with water previously obtainable only by distillation. Whereas mineral-free water produced by this means has been used successfully to replace distilled water in many chemical processes, industrial operations (Figs. 4 and 5) and in laboratory procedures, the purity of such water and its suitability for use in pharmaceutical preparations had not been investigated. This paper constitutes a summary of a preliminary investigation of the chemical composition of mineral-free water produced by an ion-exchange process, and its possible uses in pharmacy.

EXPERIMENTAL

Studies of the Chemical Purity of Mineral-Free Water.—In order to establish the chemical composition of mineral-free water produced by an ion-exchange process employing synthetic resin exchange absorbents, samples of municipal waters were analyzed for their chemical constituents following a "deionizing" treatment in exchange columns similar to those described by Myers, Eastes and Myers (3), and shown in Figs. 2 and 3.

As a preliminary study the water was examined to determine whether it passed the specifications for Aqua Distillata as defined in the U. S. P. XII. Philadelphia Tap Water (Delaware Supply), which had been rendered mineral-free by means of ion-exchange resins, was found to pass the U. S. P. specifications for appearance, dissolved solids, reaction, chloride, sulfate, ammonia, calcium and heavy metals. The carbon dioxide specification was met after aerating the sample (the original untreated contained an appreciable amount of carbon dioxide).

Samples of the water were then analyzed by Dr. G. R. Harrison of the Massachusetts Institute of Technology, by spectrographic methods. The results are shown in Table I. Sodium, copper,

TABLE I.—SPECTROGRAPHIC ANALYSIS OF MINERAL-FREE PHILADELPHIA WATER TREATED WITH AMBERLITE IR-RESINS

Element	Concentration, Mg./L.
Silicon	0.06
Calcium	0.06
Iron	0.03
Magnesium	0.016
Sodium	Less than 0.016
Copper	Less than 0.016
Manganese	Less than 0.016
Aluminum	Less than 0.016
Chromium	Less than 0.016
Zinc	Absent
Lead	Absent

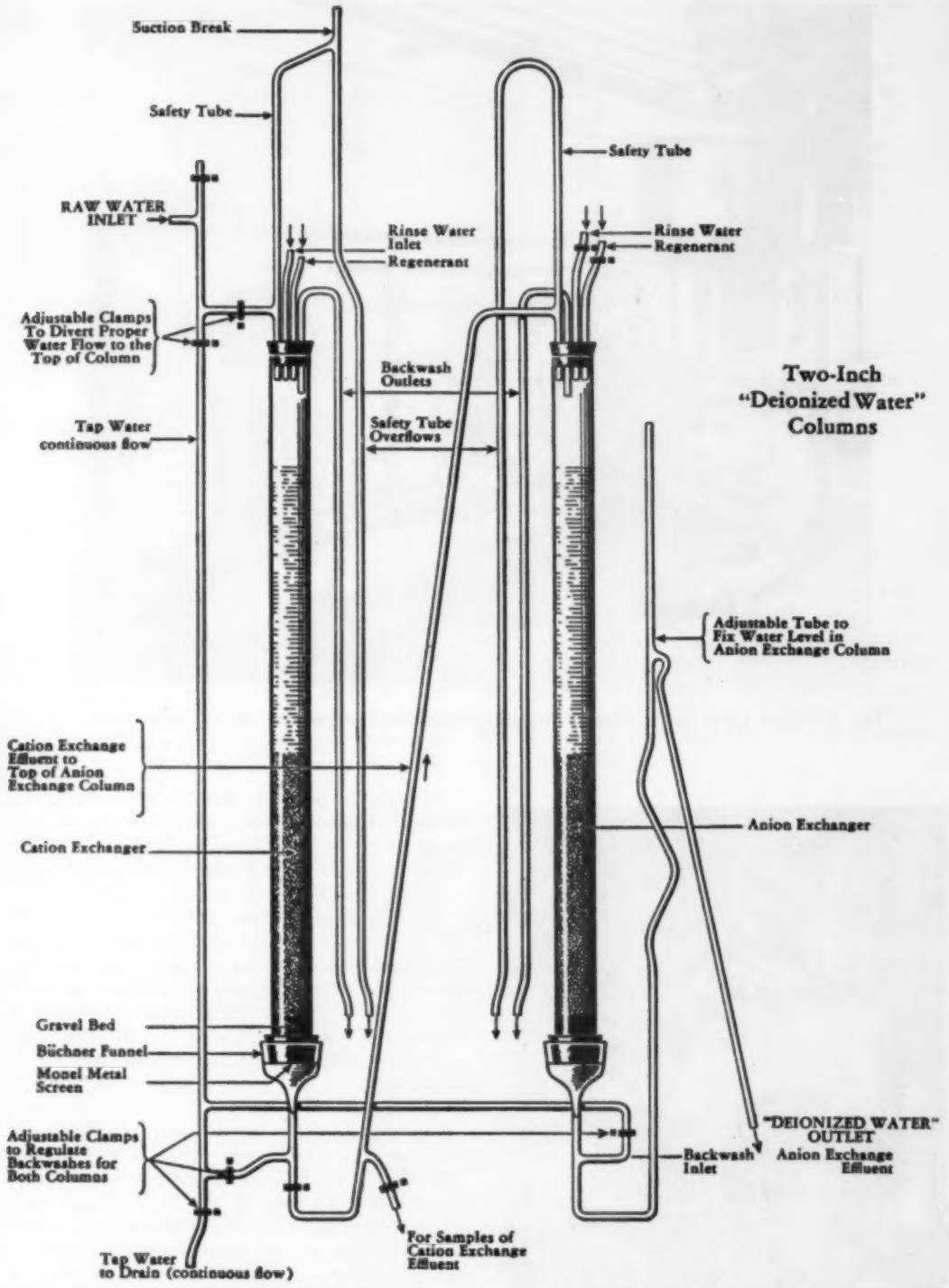


Fig. 2.—Drawing of small laboratory columns (2-inch diameter) for the preparation of mineral-free water in the laboratory.

manganese, aluminum and chromium were present but in an amount less than 0.016 mg./L. Zinc and lead were definitely absent.

The figures listed in Table I indicate an exceedingly high degree of chemical purity of the mineral-free water produced by this treatment. It may be mentioned here that colloidal silica is not removed, but there are several methods of removing silica which can be employed prior to the removal of dissolved salts by means of ion-exchange resins.

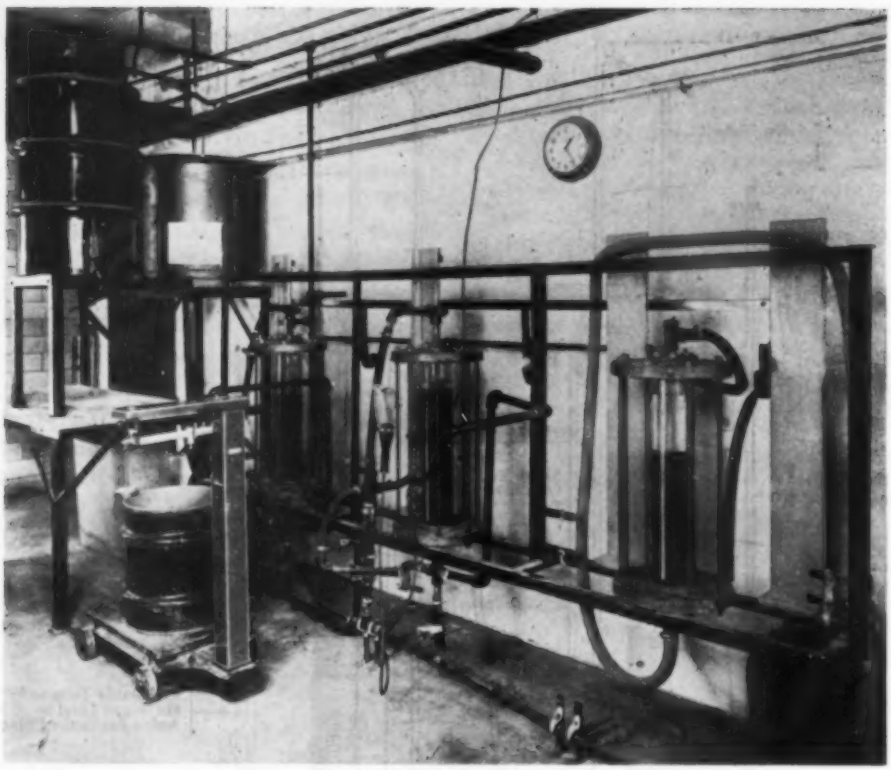


Fig. 3.—Pilot plant installation of desalting equipment, employing ion-exchange resins.

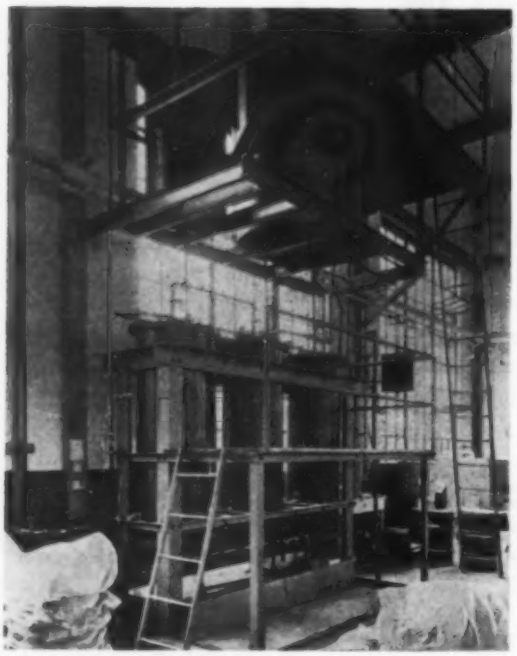


Fig. 4.—Plant scale desalter for the preparation of mineral-free water at rates as high as 2000 gal. per hour.

In order to establish that the efficiency of the removal of dissolved salts, as effected by the ion-exchange resins, is independent of the composition of the raw water, several sources of municipal water were treated. The results are shown in Table II.

Possible Contaminations Introduced by the Exchange Resins.—That the chemical purity of water produced by the ion-exchange resins is equal to that resulting from the distillation process has been shown. As a further evidence of the suitability of the treated water as prepared by this process for general pharmaceutical use, it was examined for its pyrogenic effect. It may be observed first, however, that distilled water for pharmaceutical use other than the preparation of parenteral solutions is not required to be pyrogen-free. Nor is it to be presumed that water once contaminated with pyrogenic material will be purified by the treatment with resinous exchangers, but rather that this treatment does not result in such treated water acquiring a pyrogenic effect. Normally, the pyrogenic effect of water results from the presence of complex bodies produced by bacterial or microscopic growth or their products of metabolism. Water containing such material when injected parenterally causes a systemic effect evidenced by increased temperature and shock. To prevent such occurrences, the U. S. P. XII provides a test to establish that injection water is pyrogen-free. The test is performed upon rab-

TABLE II.—DESALTING (DEIONIZING) OF MUNICIPAL WATERS BY ION-EXCHANGE RESINS

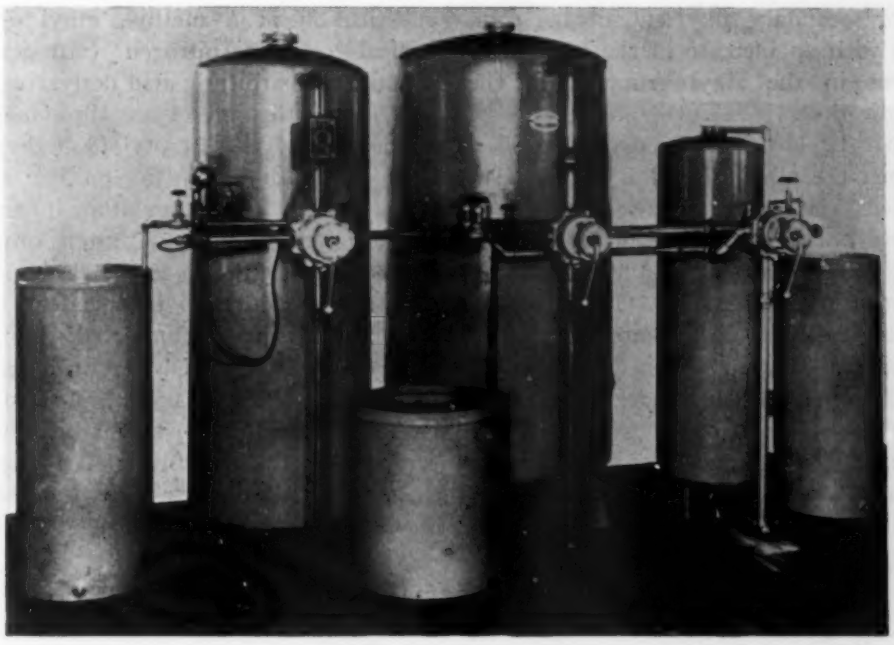
	Philadelphia, Parts per Million		Indianapolis, Parts per Million		New Brunswick, Parts per Million	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Total solids	85	Less than 10	399	Less than 10	78	Less than 10
Loss on ignition	15	.....	103	.....	29	.....
Calcium	23	Absent[a]	62	Absent[a]	9.5	Absent[a]
Magnesium	7	Absent[a]	28	Absent[a]	2.0	Absent[a]
Iron	0.02	Absent[a]	0.05	Absent[a]	0.02	Absent[a]
*p*H	6.6	5.5	8.4	5.1	9	5.2
Chloride	10	0	15	0	7	0
Sulfate	14	0	100	0	27	0
Date samples	Average value		June 1, 1942		June 10, 1942	

[a] As determined by conductometric method.

TABLE III.—PYROGENIC EFFECT

Rabbit No.	New Brunswick City Supply			Mineral-free Water from New Brunswick City Supply		
	Preliminary Av. Temp., °F.	Highest Temp. after Injection, °F.	Rise, °F.	Preliminary Av. Temp., °F.	Highest Temp. after Injection, °F.	Rise, °F.
1	102.0	103.4	1.4	101.5	102.0	0.5
2	101.9	102.5	0.6	102.4	102.1	0.0
3	101.8	102.8	1.0	101.7	101.0	0.0
4	101.9	102.4	0.5	101.8	101.9	0.1
5	101.7	102.5	0.8	101.6	101.6	0.0

bits, noting the increase of rectal temperature following the intervenous injection of the sample to be examined. As this test is an official test, and as it is a relatively sensitive reaction, it was used to establish whether or not the treatment with resinous exchangers resulted in the acquisition of pyrogenic material by solution from the exchange resins. A typical result is shown in Table III following the administration of New Brunswick, N. J., city water and mineral-free New Brunswick city water. The use of such treated or mineral-free water is not at present recommended as a means for preparing water to be used in manufacturing parenteral solutions; however, it is entirely possible that future investigation may show this also to be a practical application of the process.



Courtesy, Illinois Water Treatment Company

Fig. 5.—Typical commercial installation of desalting equipment employing resinous exchangers.

SUMMARY

Advances in the production of resin exchange absorbents have made possible the preparation by filtration procedures of mineral-free water equal in quality to that required for distilled water of the U. S. P. Ease of manipulation, low initial cost and freedom from costly maintenance recommend this method of preparing mineral-free water for many pharmaceutical uses.

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Barbituric Acid Derivatives

Relationship between Action on Smooth Muscle and Frog's Heart, and Chemical Structure*

By C. E. Powell, H. M. Lee and Edward E. Swanson†

In a previous communication (1), it was observed that there is an obvious relationship between the pharmacological action and the chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds with an increase in the number of C atoms in the alkyl group, both the anesthetic dose (M. A. D.) and the lethal dose (M. L. D.) grow relatively smaller, but when the alkyl radical is longer than 5 C atoms, the amount required to produce anesthesia or death in rats again increases. As the alkyl chain lengthens, the therapeutic index or ratio between the M. A. D. and M. L. D. appears to be gradually greater. In general, the duration of action shows a similar tendency; that is, it is shorter when the alkyl group becomes lengthened. In normal (primary) alkyl-substituted derivatives, the critical compound is the one that possesses 6 C atoms in one of the 5,5-positions; in the secondary alkyl-substituted derivatives, it is the one having 7 C atoms in one of the 5,5-positions, beyond which the duration of action begins to increase. It has been reported that the substitution of a methyl, ethyl or allyl radical on the nitrogen (nitrogen-alkyl substituted barbituric acid derivatives) (2); or the substitution of an allyl, methallyl (2-methyl-allyl) (3), crotyl (3-methyl-allyl) (4) or 1-methyl-allyl (5) on one of the 5,5-positions; or a sulfur atom (6) in place of the oxygen on the 2-C atom, obviously reduces the duration of action. This shorter duration of action is independent of the amount of drug administered. More recently, it was observed that in a series of primary and secondary alkyl-substituted barbituric acid and thiobarbituric acid compounds the hemolytic time on the sheep's blood increases as the number of C atoms increases in the substituted alkyl radical (7).

EXPERIMENTAL

The present investigation is a study of a series of 5,5-substituted barbituric and thiobarbituric acids (Table I), having the general formula:

* From the Lilly Research Laboratories, Indianapolis, Ind.

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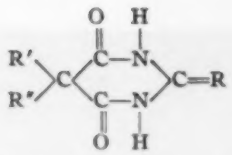
† The authors are indebted to Dr. K. K. Chen, Director of Pharmacologic Research, for his valuable suggestions and criticisms, and to Robert D. Fink for his technical assistance.



wherein R′-alkyl radical may be a primary or secondary (with 2 to 8 C atoms); R″-alkyl, an ethyl or crotyl radical; and R, a sulfur atom in place of the oxygen.

isolated muscles with Tyrode's solution. This study is concerned with the relationship between the effect on the isolated muscles (uterus and intestine) and perfused frog's heart, and the chemical structure of certain barbituric and thiobarbituric acids.

As shown in Figs. 1, 2 and 3 on the isolated rabbit's intestinal strip with 0.0005 *M* solutions, the inhibition with both the primary and secondary substituted derivatives increased as the number of C atoms increased (2 to 8) in the alkyl-substituted

TABLE I.—BARBITURIC AND THIOBARBITURIC ACID DERIVATIVES STUDIED

Number of C Atoms in Alkyl-Substituted Radical	Primary Alkyl-Substituted Derivatives	Secondary Alkyl-Substituted Derivatives
2	*Ethyl*-ethyl barbituric acid	.....
3	*n-Propyl*-ethyl barbituric acid	*1-Methyl-ethyl*-ethyl barbituric acid
4	*n-Butyl*-ethyl barbituric acid	*1-Methyl-propyl*-ether barbituric acid
5	*n-Pentyl*-ethyl barbituric acid	*1-Methyl-butyl*-ethyl barbituric acid
6	*n-Hexyl*-ethyl barbituric acid *1,3-Dimethyl-butyl*-ethyl barbituric acid	*1-Methyl-pentyl*-ethyl barbituric acid
7	*n-Heptyl*-ethyl barbituric acid	*1-Methyl-hexyl*-ethyl barbituric acid
8	.....	*1-Methyl-heptyl*-ethyl barbituric acid
2	*Ethyl*-crotyl thiobarbituric acid	.....
3	*n-Propyl*-crotyl thiobarbituric acid	*1-Methyl-ethyl*-crotyl thiobarbituric acid
4	*n-Butyl*-crotyl thiobarbituric acid	*1-Methyl-propyl*-crotyl thiobarbituric acid
5	.....	*1-Methyl-butyl*-crotyl thiobarbituric acid

These barbituric acid derivatives were tested on the isolated rabbit's intestine, isolated guinea pig's uterus and perfused frog's heart, the last according to the method of Howell and Cooke (8). Equimolecular solutions of the sodium salt of the barbituric and thiobarbituric acids were used. The hydrogen-ion concentration of each solution was adjusted to a *p*H of 9.5–10.6. The frog's heart was perfused with a buffered Ringer solution and the chain. Diethyl barbituric acid produced no inhibition, *n*-propyl-ethyl barbituric acid only a very slight action, *n*-butyl-ethyl barbituric acid a definite decrease in amplitude and finally *n*-hexyl- and *n*-heptyl-ethyl barbituric acid compounds a complete inhibition. The secondary substituted derivatives produced a similar increased inhibitory action as the number of C atoms increased (3 to 8) in the substituted alkyl radical. As shown in Fig. 4, the

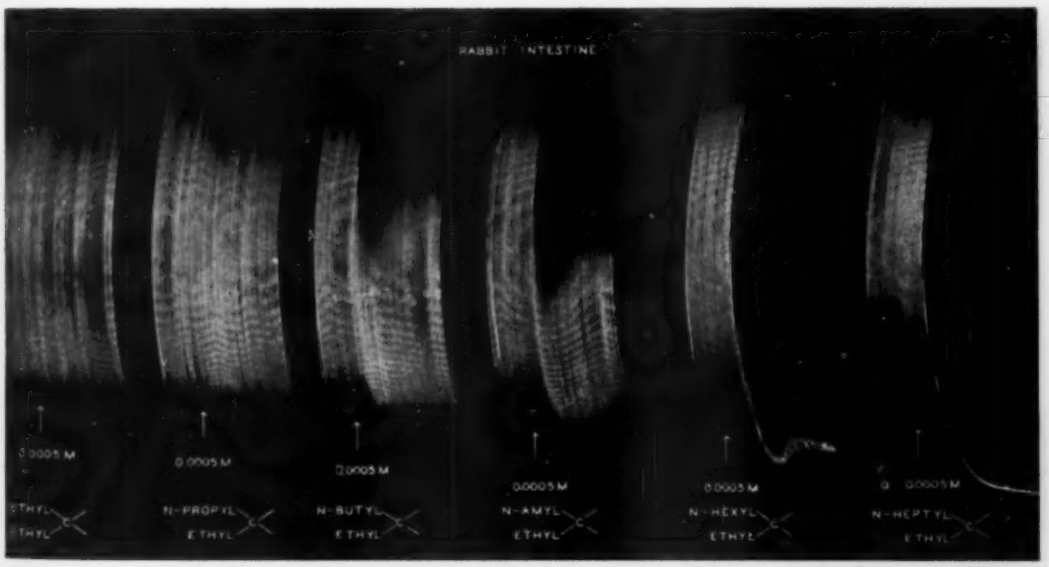


Fig. 1.—Isolated rabbit's intestinal strip in Tyrode's solution with 0.0005 *M* solutions of each compound. As the number of C atoms increases (2 to 7) in the substituted primary alkyl radical, the inhibitory action increases.

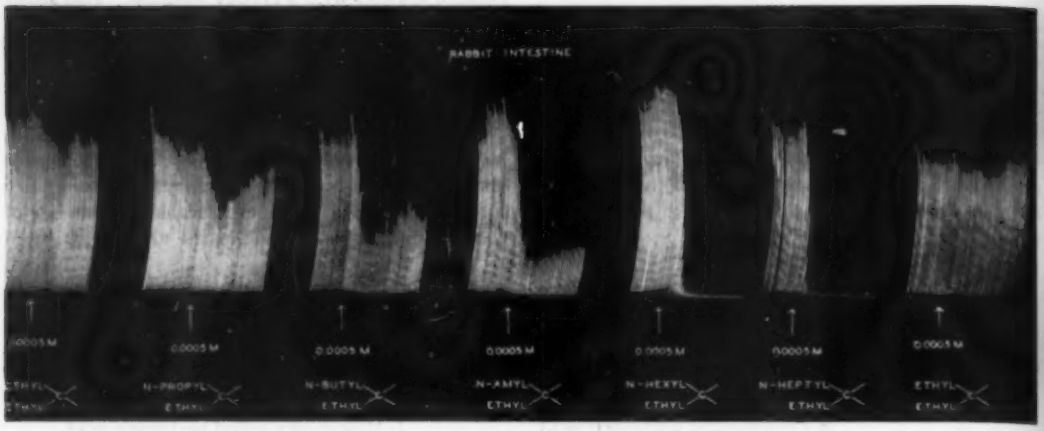


Fig. 2.—As the number of C atoms increases from 2 to 7 in the primary alkyl-substituted radical, there is a gradual increased inhibition of isolated rabbit's intestine. It is interesting to note that diethyl barbituric acid with 0.0005 *M* concentration produces very little inhibitory action with the first dose or at the end of the test.

hiobarbituric acid compounds also showed the same action; that is, as the number of C atoms increased (2 to 4), the inhibition was more effective. The secondary alkyl thiobarbituric acid derivatives produced a greater inhibition than the primary group.

On the isolated guinea pig's uterus, there was a decrease in the normal rhythm as the number of C atoms increased in the primary and secondary alkyl-substituted barbituric and thiobarbituric acid compounds. In Fig. 5 the results are shown with the primary substituted derivatives.

The same series of barbituric and thiobarbituric acid derivatives, perfused through the frog's heart, decreased the amplitude and rate of the heart. This effect was more pronounced as the alkyl-substituted chain increased in length. The results with the primary alkyl-substituted derivatives are summarized in Fig. 6.

Not all barbituric acid compounds have the characteristic hypnotic and anesthetic properties. In previous reports (9, 10) it was observed that sodium 1,3-dimethyl-butyl-ethyl barbiturate was a powerful convulsant. This aberrant action was more extensively studied by Swanson and Chen (11) who revealed that convulsions occurred in warm-blooded animals but depression in amphibians (frogs and toads). This compound was also tested on the isolated rabbit's and frog's intestinal strips and

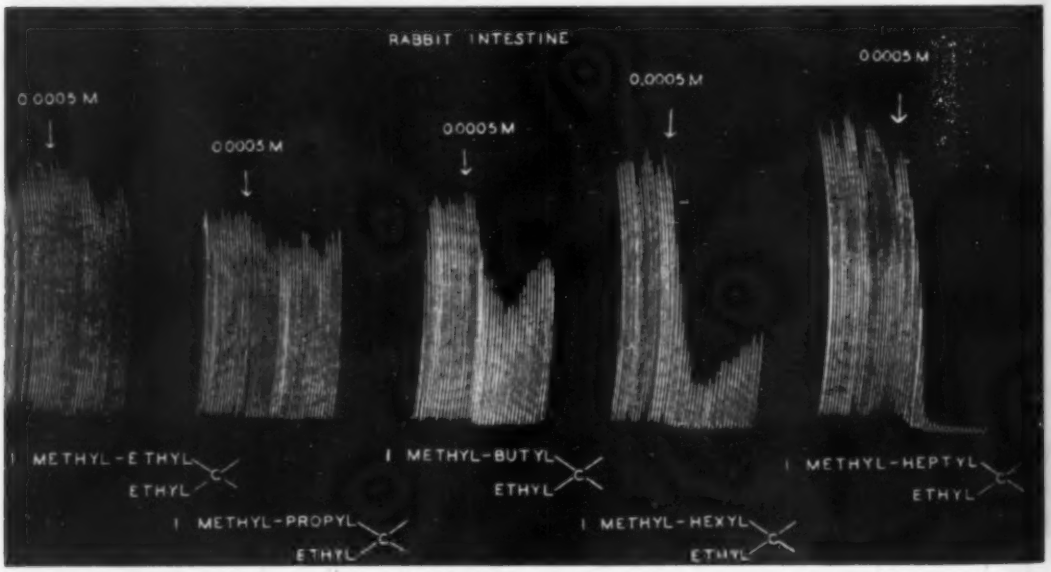


Fig. 3.—With 0.0005 *M* solutions of the secondary alkyl-substituted derivatives an isolated rabbit's intestinal strip shows distinct inhibition as the number of C atoms increases in the alkyl chain from 3 to 8.

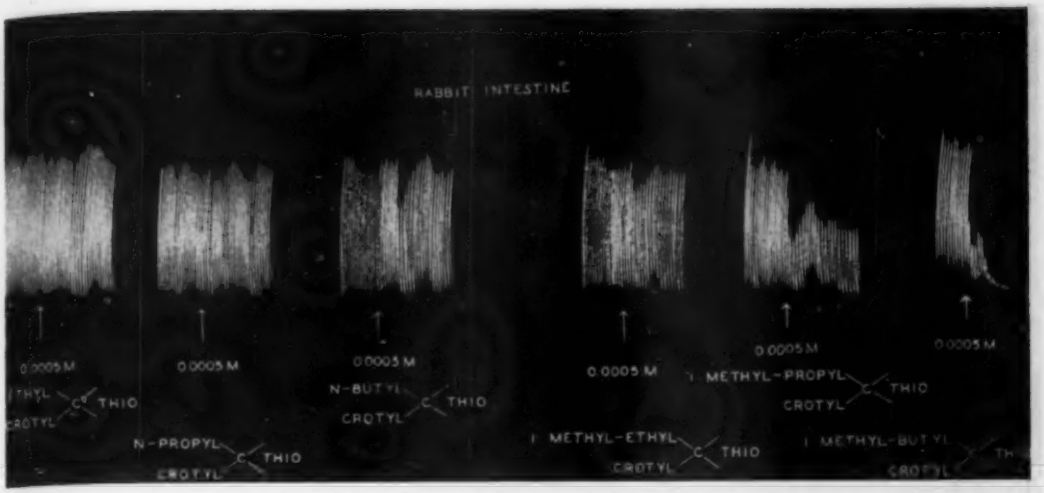


Fig. 4.—The action of 3 primary and 3 secondary alkyl-substituted thiobarbituric acid compounds on the isolated rabbit's intestinal strip is shown. With 0.0005 *M* solutions, the secondary series shows more inhibition than the primary derivatives.

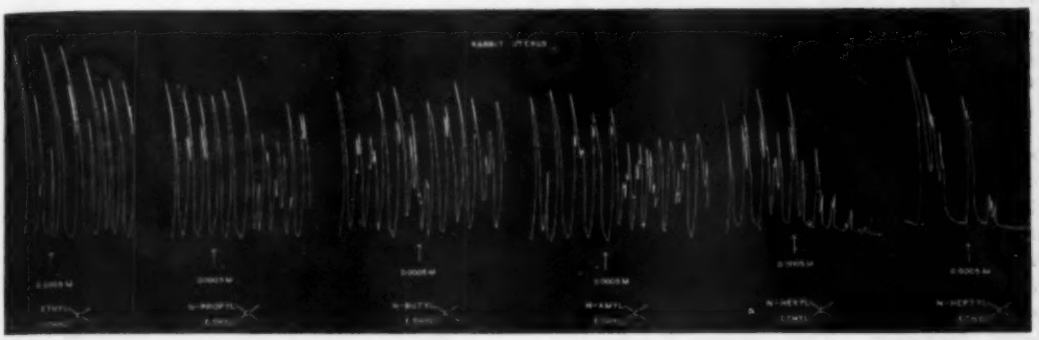


Fig. 5.—With 0.0005 *M* solutions the sedative action on the isolated rabbit's uterus gradually increases as the number of C atoms increases (2 to 7) in the primary alkyl-substituted radical.

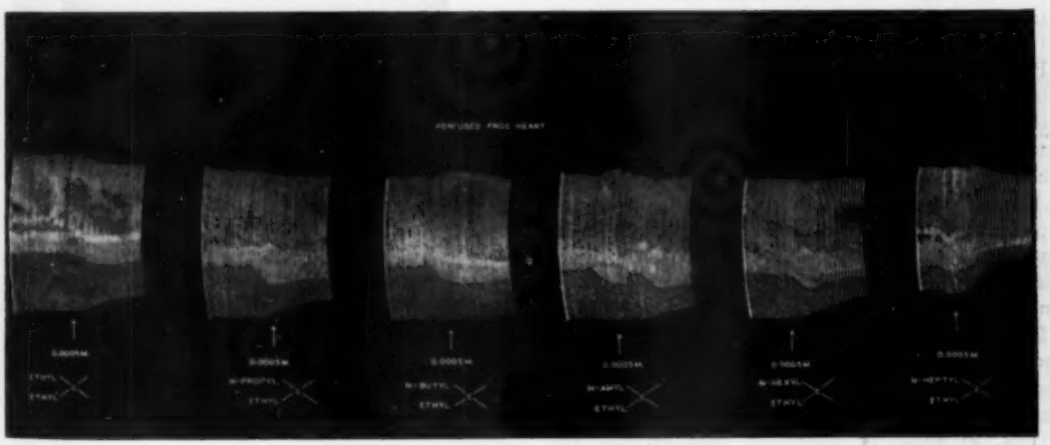


Fig. 6.—As the number of C atoms increases in the substituted alkyl chain (2 to 7), the amplitude and rate of the heart decrease in a perfused frog's heart with buffered saline solution.

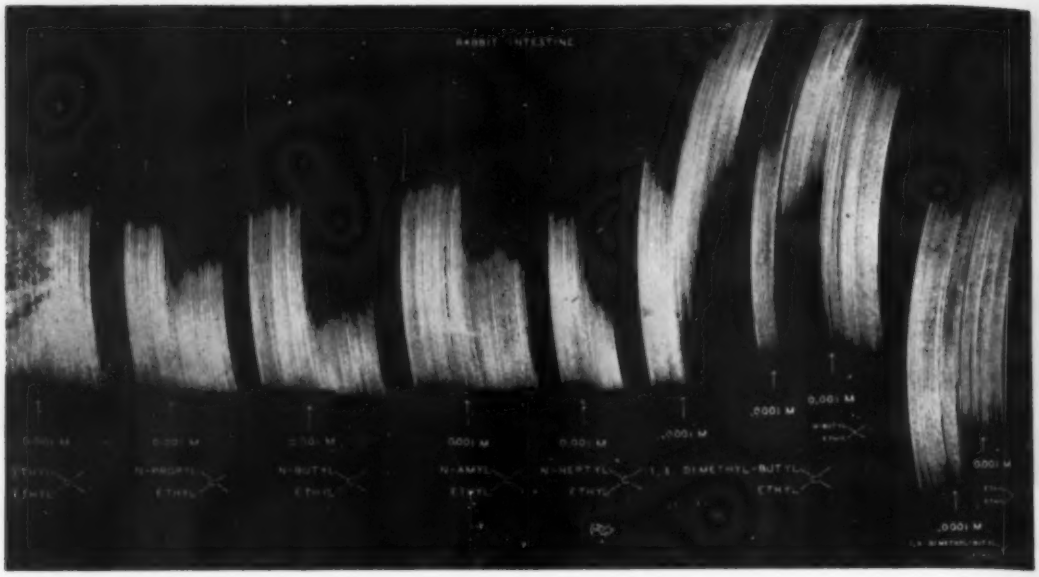


Fig. 7.—The inhibitory action of the isolated intestine of a rabbit increases as the number of C atoms increases from 2 to 7. Sodium 1,3-dimethyl-butyl-ethyl barbiturate, a powerful convulsant in intact warm-blooded animals, produces stimulation of the intestine. This derivative is an isomer of *n*-hexyl-ethyl barbituric acid and 1-methyl-butyl-ethyl barbituric acid, both of which are true hypnotics and inhibit the isolated intestine. As shown in this tracing, the stimulation of sodium 1,3-dimethyl-butyl-ethyl barbiturate is inhibited by *n*-butyl-ethyl barbituric acid but not by diethyl barbituric acid with a 0.001 *M* concentration.

perfused frog's heart. It is interesting to note that on the isolated rabbit's intestine, distinct stimulation was observed (Fig. 7), and, furthermore, this stimulation was overcome or inhibited by one of its isomers, *n*-hexyl-ethyl or 1-methyl-butyl-ethyl barbituric acid. On the isolated frog's intestine and perfused frog's heart, this convulsant derivative produced depression. Thus, sodium 1, 3-dimethyl-butyl-ethyl barbiturate acts as a stimulant on isolated smooth muscle and a convulsant when administered hypodermically to warm-blooded animals, but is a depressant to cold-blooded animals (isolated frog's intestine, perfused frog's heart or intact frogs and toads).

From several angles, these results are interesting. First, the barbiturates, *n*-hexyl-ethyl and 1-methyl-butyl-ethyl barbituric acids, which are isomers of this convulsant compound, have typical inhibitory action on the isolated intestine and uterus of warm-blooded animals (rabbit and guinea pig). From a chemical point of view, the deviation of this derivative was not predictable. Second, the stimulating action of 1,3-dimethyl-butyl-ethyl barbituric acid is apparently antagonized by one or both of its isomers or any other true depressant barbiturate. Third, the difference of response between isolated warm-blooded smooth muscles and cold-blooded smooth muscles and perfused heart of frogs is striking. Such examples, indeed, are not uncommon. Thus, in sufficient quantities both cocaine and harmine are convulsants in warm-blooded animals but are depressants in frogs (12, 13). It is well known that morphine is stimulating to cats but depressing to other animals.

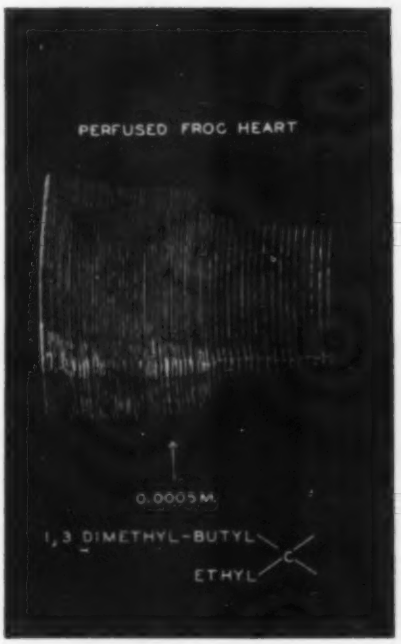


Fig. 8.—In the perfused frog's heart this convulsant, sodium 1,3-dimethyl-butyl-ethyl barbiturate, acts as a sedative—thus decreasing the amplitude and rate of the heart.

CONCLUSIONS

1. A series of primary and secondary barbituric acid and thiobarbituric acid compounds have been studied on the isolated smooth muscle of rabbits, guinea pigs and frogs, and on the perfused frog's heart.

2. As the number of C atoms increased in the substituted alkyl chain, the inhibition or sedative action increased on the isolated intestine of rabbits and frogs and the isolated uterus of guinea pigs. The same degree of depression was observed in the perfused frog's heart.

3. Sodium 1,3-dimethyl-butyl-ethyl barbiturate, a convulsant when injected in warm-blooded animals and a depressant to cold-blooded animals, produced stimulation or contraction on the isolated intestinal strips of rabbits, but depressed the isolated frog's intestine and perfused frog's heart.

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The Comparative Rate of Gastrointestinal Absorption of Barbital, Sodium Barbital and Elixir of Barbital N. F. VII*

By Victor P. Seeberg and James M. Dille

Barbiturates are generally administered orally in the form of tablets, capsules or elixirs using either the acid form of the barbiturate or the sodium salt. Absorption from the gastrointestinal tract is generally considered to be satisfactory (1), but differences in the rate of absorption are to be expected between different pharmaceutical preparations. The experiments reported here show these differences.

EXPERIMENTAL

The general experimental procedures used were as follows: The preparation being studied was administered orally to a 24-hr. starved cat. A period of one-half hour was allowed to elapse after administration during which the onset and degree of depression were noted. At the end of this period the cat was killed by exsanguination. The blood and the contents of the stomach, intestine and colon were assayed separately for barbital. Comparison of these values indicates the rate of absorption. Barbital was selected rather than one of the other barbiturates because the dose is large and the resulting higher concentration in the material assayed led to more accurate determinations. The following forms of barbital and sodium barbital were used.

Tablets of Barbital and Sodium Barbital.—Five-grain tablets of barbital and five-grain tablets of sodium barbital of a well-known brand were purchased on the open market from fresh stock in sealed bottles of 100 tablets. Preliminary experiments on the rate of disintegration of the tablets were made by shaking them in a 1% hydrochloric acid solution on a mechanical shaker. Rapid, but somewhat variable, disintegration times were found. The mean disintegration time for 10 tablets of barbital was found to be 6 min. with a range of 3 to 10 min. Tablets of sodium barbital gave about the

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same values. This factor is of importance in the use of this form of medication, but practically the disintegration is rapid enough to make this variable of minor importance when viewed in the light of the larger variable of absorption; and so to make it easy to administer an accurate dose, the tablets were crushed and a weighed quantity of the crushed tablet material administered. Administration was also facilitated because the crushed material could be given by stomach tube with the assurance that it would reach the stomach. A whole tablet or portion of a tablet might remain unswallowed or lodged in the esophagus.

The crushed tablets were assayed for barbital. Representative samples of the crushed samples were dissolved in water, made up to volume, aliquots taken, acidified and extracted three times with chloroform. The combined chloroform extracts were evaporated to dryness on a water bath, cooled and dissolved in a known volume of chloroform. The barbital in the chloroform solution was determined colorimetrically using the method of Dille and Koppanyi (2). The crushed material from the barbital tablets was found to contain 86.6% barbital and the crushed material from the sodium barbital tablets was found to contain 73.9% barbital. This closely checked the labeled amounts of barbital.

Elixir of Barbital.—The elixir was made up accurately according to directions in the National Formulary VII. (The monographs for Elixir of Barbital are the same in the N. F. VI and the N. F. VII). The quantity of barbital in this preparation was thus known, and the volume containing the proper dose could therefore be easily determined.

Capsules of barbital and sodium barbital were not used because of the introduction of the factor of dissolution of the capsule. After the contents of the capsule are released, the rate of absorption of the dispersed contents would not differ significantly from that of the disintegrated tablet. The factors of the rate of disintegration of the tablets and the time of dissolution of the capsule shells have thus been avoided in these experiments.

PROCEDURES FOR THE DETERMINATION OF ABSORPTION

In order to make certain that the gastrointestinal tract was empty, or nearly so, the cats were not allowed to have food for 24 hrs. before the experiment. In order to simulate the conditions in which these preparations are generally used, 15 cc. of water per Kg. was given with the drug. In the case of the administration of tablets, the weighed quantity of the crushed tablet was placed in a 30-cc. syringe and about one-third of the water to be given drawn into the syringe and shaken to form a suspension. The syringe was then inserted into the end of a stomach tube which had meanwhile been placed in position by an assistant. The suspension was injected and the remainder of the water used to wash the adhering particles in the syringe and the stomach tube into the stomach. The dose used was 270 mg. of barbital per Kg. which amounted to 311 mg. of the crushed barbital tablets. This same dose amounted to 365 mg. of the crushed sodium barbital tablets per Kg.

The elixir was given in the same way as the tablets. Eight cubic centimeters of the elixir, which contained the standardized dose of 270 mg. of barbital per Kg., was administered, followed by water. The volume of the elixir was subtracted from the 15 cc. of water per Kg. in order to keep the volume of fluid administered equivalent in all cases.

Twenty-five minutes after administration, the degree of depression was estimated according to the following scale:

1. No observable depression.
2. Animal able to walk but staggers.
3. Animal unable to stand, but able to lift head.
4. Animal unable to lift head, but corneal reflex present.
5. Respiratory failure.

After making this observation the animal was anesthetized in an anesthesia box with ether. The carotids were isolated and, exactly 30 min. after the administration, cut. The blood was collected in an oxalated beaker for analysis. The abdomen was opened and double ligatures carefully placed to isolate the stomach, intestine and colon. Each portion was then removed by cutting between the ligatures and the contents carefully and thoroughly washed out with approximately 150 cc. of water and assayed for unabsorbed barbital.

THE ASSAY OF THE BLOOD AND GASTROINTESTINAL RESIDUE FOR BARBITAL

Blood.—The blood was assayed for barbital by the method of Koppanyi, *et al.* (3), with modification in the quantities of reagents suggested by Kozelka and Tatum (4). This method is based on the precipitation of the proteins of the blood by the Folin-Wu procedure, and the extraction of the protein-free filtrate with chloroform. The estimation of the barbital in the chloroform solution is made by comparing the color produced by the addition of cobaltous acetate and isopropylamine reagents to the color produced by a similarly treated standard solution of barbital.

Gastrointestinal Residue.—The residual contents of the section of the gastrointestinal tract and the washings were treated, with some modification, like blood. To 150 cc. of the material were added 25 cc. of 20% sodium tungstate solution and 50 cc. of 1.33 *N* sulfuric acid. After shaking, the mixture was made up to 250 cc. and allowed to stand 24 hrs. The precipitate was then filtered out and an aliquot of the filtrate extracted three times with chloroform. The chloroform extracts were combined and evaporated to dryness. The residue was dissolved in a known volume of chloroform and the chloroform solution assayed for barbital by comparing the color produced by the addition of cobaltous acetate and isopropylamine reagents to the color produced by a similarly treated standard solution of barbital.

RESULTS AND DISCUSSION

Results given in Table I and Fig. 1 show that after a half-hour an average of 28.6% of barbital from the crushed sodium barbital tablets, an average of 69.0% of barbital from the crushed barbital tablets and an average of 74.6% of barbital from the elixir remained in the gastrointestinal tract unabsorbed. These variations are also reflected in the values for barbital concentrations in the blood, and with the degree of depression observed with sodium barbital and barbital. The depression after the administration of the elixir was proportionally greater than would be expected from the blood level of the barbital. This could be due to the effect of the alcohol in the elixir. About 2.7 cc. of alcohol per Kg. was introduced in the elixir. The paralytic dose for cats by mouth is 4 cc./Kg. (5). Therefore some depression would be expected from the alcohol, and this would be synergistic with the depression produced by the barbital.

The question arises as to whether the difference in absorption rate between the tablets of barbital and sodium barbital is due to the difference in solubility of the barbital and the sodium barbital. To answer this, a loop experiment was performed using the entire ligated small intestine as a closed loop. The concentrations of the drugs were 0.72% for barbital and 0.8% for sodium barbital. These concentrations were low enough so that both drugs were completely in solution and yet equal in barbital content. Both solutions were made isotonic to blood by the addition of the proper quantity of sodium chloride according to the formula in Powers (6). Under light ether anesthesia, each of one group of three cats was given 150 mg. of sodium barbital per Kg. by direct injection into the ligated intestine. These two doses are equal in barbital content. After a period of 30 min., the animals were lightly anesthetized with ether, killed by bleeding and the blood assayed for barbital. The intestinal loop was removed and the contents assayed for unabsorbed barbital. The results shown in Table II show that the amount of barbital in the blood is about the same in both cases, and the amount of barbital recovered

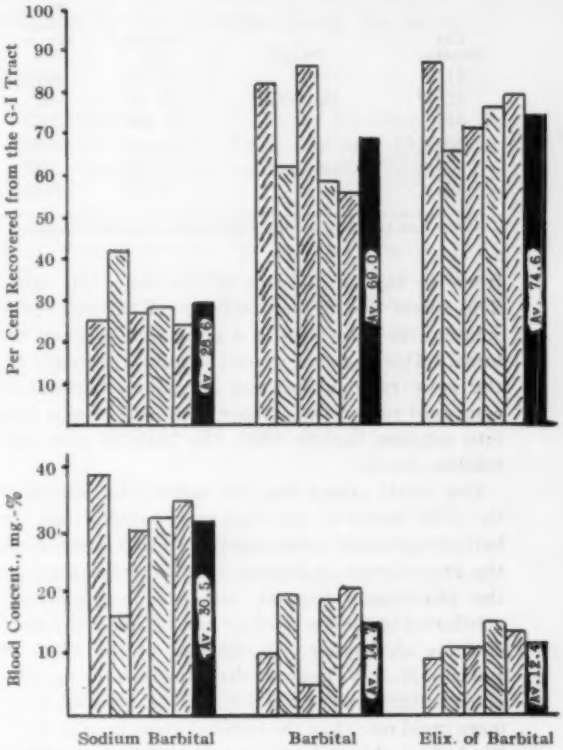

Fig. 1.—The percentage of barbital recovered from the entire gastrointestinal tract, and the blood concentration of barbital one-half hour after the oral administration of the equivalent of 270 mg. of the preparation per Kg.

TABLE I.—THE QUANTITIES OF BARBITAL REMAINING IN THE STOMACH, INTESTINE AND COLON, AND THE LEVEL OF BARBITAL IN THE BLOOD ONE-HALF HOUR AFTER THE ORAL ADMINISTRATION OF THE PREPARATIONS

Cat Number	Weight, Kg.[a]	Prepn. Admin.	Total Amt. Admin., Mg.	Stage of Depression	Stomach, Recovered Mg.	Stomach, Recovered %	Intestine, Recovered Mg.	Intestine, Recovered %	Colon, Recovered Mg.	Colon, Recovered %	Total, Recovered Mg.	Total, Recovered %	Blood Conc,, Mg., %
24	2.66	Crushed	718	4	79	11.0	74	10.3	25	3.4	178	24.8	38.7
25	3.65	tablets	985	3	300	30.5	96	9.8	..	...	396	40.2	17.4
37	3.23	of so-	872	4	198	22.7	29	3.3	..	...	227	26.0	29.8
52	2.17	dium bar-	586	4	91	15.5	72	12.3	Tr.	...	163	27.8	32.6
53	2.84	bital	767	4	110	14.3	65	8.4	12	1.6	187	24.4	34.1
23	3.70	Crushed	999	2	806	80.7	21	2.1	Tr.	...	827	82.7	9.8
28	2.40	tablets	648	2	382	59.0	20	3.1	6	0.9	408	62.9	19.5
33	2.66	of bar-	830	2	701	84.5	11	1.3	..	...	712	85.8	4.2
50	2.85	bital	769	2	429	55.8	17	2.2	..	...	446	57.9	19.7
51	1.94		524	3	273	52.1	18	3.4	..	...	291	55.5	20.3
22	3.17	Elixir of	856	3	666	77.8	25	2.9	Tr.	...	691	80.7	9.4
26	1.10	Barbital	297	4	167	56.2	27	9.0	2	0.7	196	65.9	11.3
38	2.22		599	3	400	66.8	29	4.9	...	...	429	71.6	11.3
48	2.47	N. F. VII	667	4	463	69.4	44	6.6	2	0.3	509	76.2	16.0
49	2.51		677	3	524	77.4	4	0.6	6	0.9	534	78.9	14.0

[a] All doses were equivalent to 270 mg. of barbital per Kg.

TABLE II.—THE RECOVERY OF BARBITAL FROM THE LIGATED INTESTINE AND THE BLOOD CONCENTRATION OF BARBITAL ONE-HALF HOUR AFTER THE ADMINISTRATION OF 135 MG. OF BARBITAL PER KG. AND 150 MG. OF SODIUM BARBITAL PER KG. EQUAL DOSES BY INJECTION INTO THE LIGATED INTESTINE

Cat Number	Drug[a]	Weight, Kg.	Total Amt. Admin., Mg.	Total Amt. Recovered, Mg.	% Recovered	Blood Conc., Mg., %	pH of Intestinal Contents When Introduced	pH of Intestinal Contents When Recovered
41	Barbital	2.24	302	5.0	1.6	12.4	6.3	6.3
42		3.45	465	13.2	2.8	13.5	6.3	6.8
44		1.80	243	22.2	9.0	15.9	6.3	6.7
40	Sod. barb.	3.03	408	20.0	4.9	15.7	10.0	7.8
43		2.22	300	11.6	3.9	14.9	10.0	8.0
39		2.28	308	6.0	1.9	13.6	10.0	7.0

[a] The two forms of barbital are both in isotonic solution, are equal in barbital content and were made isotonic to blood.

from the ligated intestine is also about the same. This shows that if the two forms of barbital are in solution the absorption in a given time is about the same. This explains, in part at least, the reason for the more rapid absorption of sodium barbital as compared to barbital. After administration it goes into solution rapidly while the barbital goes into solution slowly.

One would expect that the barbital in solution in the elixir would be absorbed more rapidly than the barbital given in tablet form. Indeed, aside from the convenience of having a liquid preparation at the physician's disposal, one of the advantages attributed to the use of elixir medication is the more effective absorption. In the case of the Elixir of Barbital N. F. VII our results show that the barbital given in the elixir is not absorbed at a significantly more rapid rate than the barbital given in solid form. We believe this to be due to some substance in the elixir which delays the emptying time of the stomach. This is based on the observation that the stomach was found to be distended and filled with the elixir (and the water given with it) when the experiment was terminated. When the barbital was given, the stomach was found to be collapsed and it was apparent that most of the suspended material had passed into the intestine. The suspended barbital was poorly soluble and particles of barbital were seen when the intestine was opened.

There is the possibility that the volatile oils and vanillin which are present in the N. F. VII Elixir of Barbital are the cause of the delayed emptying time. These substances are known to depress stomach activity and delay emptying time in all but the smaller quantities. Calculations show that in one dose of Elixir of Barbital N. F. VII there is a total of 0.0318 cc. of volatile oils. These amounts are below the U. S. P. doses, and it does not seem that this is the cause of our observation.

There is also the possibility that the alcohol in the elixir would have this effect, but we suspect that the offending material in the elixir is glycerin. The U. S. P. XI dose of glycerin is 4 cc. The N. F. VII dose of the elixir includes 2.6 cc. of glycerin but since this dose has only 140 mg. of barbital it is likely that more than the indicated dose of the elixir would be taken. The U. S. P. XI dose is 300 mg. and so if the U. S. P. dose were prescribed 6.0 cc. of glycerin would be ingested. This is already above the U. S. P. XI dose of glycerin. It is also possible that several times the U. S. P. XI dose of barbital would be administered with a consequently greater possibility of delaying the emptying of the stomach. A dose of 0.9 Gm. (15 grains) of barbital is not uncommon and if given in the form of the elixir would be accompanied by 16.6 cc. (over one-half ounce) of glycerin. We have been unable to find any reports on the action of these amounts of glycerin on the emptying time of the stomach, but since it is possible that it is responsible for the effect we have observed we are planning experiments to determine its action.

The Elixir of Barbital N. F. VII is therefore a somewhat illogical preparation, for while it does furnish a liquid dosage form which at times might be more convenient for the physician to administer, it does not bring about a more rapid absorption of the barbital. If an elixir of barbital is regarded as a necessity by the medical profession, studies should be made to improve it based on pharmacological criteria. However, an even better suggestion, in view of the excellent absorption of sodium barbital, would be for the pharmaceutical profession to devise a properly flavored liquid preparation of sodium barbital to offer to the medical profession.

CONCLUSIONS

1. Tablets of sodium barbital administered after crushing are absorbed more rapidly from the gastrointestinal tract of 24-hr. starved cats than crushed tablets of barbital or barbital administered in the form of the Elixir of Barbital N. F. VII.

2. Crushed tablets of barbital are absorbed at about the same rate as the elixir.

3. After oral administration only small amounts of the drug reach the colon indicating that absorption takes place mainly in the small intestine.

4. Absorption of isotonic solutions from the ligated intestine is about the same for barbital and sodium barbital provided that both are in solution.

5. Absorption of barbital after administration of the Elixir of Barbital N. F. VII is

much slower than was expected. While depression was greater than the blood level of barbital would indicate, this can be explained by the presence of alcohol in the elixir. The delayed absorption of the barbital in the elixir probably occurs because the glycerin present delays the passage of the elixir into the intestine from the stomach.

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A Rapidly Absorbed Elixir of Sodium Barbital*

By Victor P. Seeberg

In a previous paper (1) we have reported the rates of absorption of barbital, sodium barbital and Elixir of Barbital N. F. VII administered orally to cats. After a half-hour absorption period, an average of 28.6% of barbital from the crushed sodium barbital tablets, an average of 69.0% of barbital from the crushed barbital tablets and an average of 74.6% of barbital from Elixir of Barbital N. F. VII remained unabsorbed in the gastrointestinal tract. These variations were reflected in the values for barbital concentrations in the blood and with the degree of depression in the test animals at the termination of the absorption period.

The slow absorption of the elixir was in contrast to the general belief that liquid forms of medication are absorbed more rapidly than solid forms. This effect was apparently due to some substance in the elixir which delayed the emptying of the stomach. A consideration of the ingredients of the elixir led to the conclusion that the glycerin (amounting to about 62%) was probably responsible for the delay of emptying of the stomach. This made it evident that a glycerin-free elixir should be studied from the standpoint of the absorption of the barbiturate contained in it and led to the development of a glycerin-free liquid preparation of sodium barbital, and this paper is a report of experiments on its rate of absorption.

EXPERIMENTAL

An elixir of sodium barbital was prepared as follows:

Sodium barbital	38.0 Gm.
Caramel	20.0 Gm.
Compound spirit of vanillin	30.0 cc.
Syrup	375.0 cc.
Purified talc	30.0 Gm.
Alcohol, Distilled water, each a sufficient quantity to make	1000.0 cc.

To 500 cc. of equal parts of alcohol and water, add the compound spirit of vanillin and the syrup, mix the talc intimately with the liquid and filter, returning the first portions of the filtrate until a clear liquid is obtained. Then dissolve the sodium barbital and caramel and add sufficient alcohol and water to make the product measure 1000 cc.

Filtration with talc was found necessary in order to make a clear preparation after the compound spirit of vanillin was added. This procedure is the same as that used in Aromatic Elixir U. S. P. in which compound spirit of orange is added to a similar concentration of sugar and alcohol in water. The flavoring and coloring agents are the same as those used in the N. F. preparation, and the alcohol concentration is 22–24%, the usual concentration of elixirs. There is little difference in color and flavor between this preparation and the Elixir of Barbital N. F. VII.

The preparation was administered by stomach tube to cats which had been deprived of food for 24 hrs. A dose of 300 mg./Kg. of sodium barbital was given, which is equal to 270 mg. of barbital. Suffi-

* Received January 8, 1943, from the Department of Pharmacology, College of Pharmacy, University of Washington, Seattle, Wash.

TABLE I[a]

Cat No.	Wt., Kg.	Prepn. Adm.	Total Sod. Barb. Adm., Mg.	Stage of Dep.	Stomach, Recovered Mg.	%	Intestine, Recovered Mg.	%	Colon, Recovered Mg.	%	Total, Recovered Mg.	%	Blood Concentration, Mg., %
55	1.81	Elix.	543	4	250	46.0	28	5.2	...	...	278	51.2	23.3
56	1.45	of	435	5	148	34.0	31	7.1	7	1.6	186	42.8	15.8
57	2.93	So-	879	4	243	27.6	103	11.7	...	...	346	39.4	21.4
58	3.37	dium	1011	5	263	26.0	33	3.3	6	0.6	302	29.8	22.0
59	2.65	Bar-	795	4	366	46.0	21	2.6	...	...	387	48.7	16.0
62	1.41	bital	423	4	154	36.4	12	2.8	...	...	166	39.2	22.1

[a] The quantities of barbiturate remaining unabsorbed in the stomach, intestine and colon, and the level of barbital in the blood 1/2 hr. after the oral administration of 300 mg./Kg. of sodium barbital in the form of a proposed new Elixir of Sodium Barbital. Recoveries are given in terms of sodium barbital. Blood concentrations are all given in terms of barbital.

cient water was used to wash the syringe and stomach tube to make the total fluid volume administered 15 cc./Kg. At the end of 1/2 hr., the degree of depression was noted, the cat etherized and killed by exsanguination. The contents of the stomach, intestine and colon were analyzed separately for the unabsorbed barbiturate and the concentration of barbital in the blood determined. The procedure for analysis consisted of extraction of the barbiturate from blood and analyzing colorimetrically by the method of Koppanyi, *et al.* (2), with modification in the quantities of reagents suggested by Kozelka and Tatum (3). The gastrointestinal contents were extracted and analyzed by a modification of the procedure for blood. The degree of depression was estimated according to the following scale:

1. No observable depression.
2. Animal able to walk but staggers.
3. Animal unable to stand, but able to lift head.
4. Animal unable to lift head; corneal reflex present.
5. Deep narcosis; corneal reflex absent.
6. Respiratory failure.

The results of six such experiments with elixir of sodium barbital are given in Table I.

These results indicate that after a half hour of absorption an average of 41.8% of sodium barbital from elixir of sodium barbital remained unabsorbed in the gastrointestinal tract. The results for Elixir of Barbital N. F. VII showed that with this preparation 74.6% of the administered barbital was unabsorbed (1). These values are also reflected in the concentration of the barbiturate in the blood and in the degree of depression observed at the end of the absorption period. It was also observed that the stomach was never distended or the pyloris contracted as was observed with Elixir of Barbital N. F. VII.

CONCLUSION

A new elixir of sodium barbital containing no glycerin was found to be absorbed rapidly from the gastrointestinal tract of cats and therefore possesses advantages over the glycerin-containing elixir of barbital.

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Use of the Latent Period in the Assay of Ergonovine on the Isolated Rabbit Uterus*,†

By Bert J. Vos, Jr.

Attempts to measure the ergonovine content of ergot colorimetrically give results which are in general too high. Presumably this is caused by inactive water-soluble alkaloids which are carried along with the ergonovine in the extraction process (1). Until more simple effective methods of separating ergonovine are developed the biological assay of ergonovine will retain an important role in the testing of ergot. Of the various methods for the biological assay of ergonovine which have been suggested in the literature, only that of deBeer and Tullar (2) is presented in sufficient detail to permit an estimate of its inherent reli-

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† It is a pleasure to acknowledge the assistance of C. I. Bliss, Connecticut Agricultural Experiment Station, in outlining the method for computing the standard error of the assay, and that of D. C. Grove, Drug Division, Food and Drug Administration, in preparing the ergonovine solutions used in this study.

ability. The following method, while no more specific than other methods for the biological assay of ergonovine, is presented because of the increased precision it affords. It is based on the fact that large doses of ergonovine stimulate contraction of the isolated rabbit uterus more promptly than small doses. A similar principle has been used by Lehman and Paff for the assay of digitalis on the embryonic chick heart (3).

EXPERIMENTAL

At the beginning of this study uteri from normal adult female rabbits showing vaginal hyperemia were used. Following the work of Wick and Powell (4) a change was made to the use of immature rabbits (2.2 to 2.6 Kg.) which were injected subcutaneously with 50 γ of estrone every other day for a total usually of six doses. This procedure increased the percentage of rabbits having uteri with which assays could be obtained from about 66% to over 90% and materially reduced the amount of ergonovine needed. After removing the uterus from the animal, a segment about 2 cm. long was taken for the assay, and the remainder was stored in a physiological salt solution at 5° C. Segments from this refrigerated uterus were found suitable for assay purposes as long as 48 hrs. after removal from the rabbit. The physiological salt solution used as the environment of the uteri during both storage and assay was that of Van Dyke and Hastings (5) modified by the addition of 0.05% dextrose. The assay was conducted in a smooth muscle bath of 100 cc. capacity maintained at 37.5 ± 0.2° C. Mixing and oxygenation were accomplished by bubbles of 5% CO_2-95% O_2 rising in a side tube similar to that in the bath described by Harne (6). By keeping the number of bubbles per minute constant a uniform rate of mixing was maintained at all times. A kymographic record was taken of the contractions of the uterus.

The standard with which unknown solutions were compared consisted of a 0.00271% solution of ergonovine acid maleate in distilled water. One cubic centimeter of this is equivalent to 0.02 mg. of the free base. The dose of the standard, usually about 1 cc., was adjusted so that it caused the uterus to contract after a latent period of from 2 to 5 min. The latent period, which was used as a criterion of potency, was measured on a stop watch to the nearest second and was taken as the interval between the beginning of the addition of the ergonovine to the bath and the first contraction of the uterus. Uteri are relatively refractory to ergonovine for the first few doses and the latent period decreases precipitously. Accordingly the first two or three additions of ergonovine to the bath were restricted to "range finding" with the standard solution. Following this the assay proper was begun. In conducting an assay doses of the standard were alternated with doses of the unknown. The doses of the standard were kept constant while those of the unknown were varied in size so that some gave shorter latent periods and others longer latent periods than the standard. It is important to run the assay on a definite time schedule. The bath was always flushed out 1 min. after the first contraction of the uterus, and the following dose was added at a regular interval after changing the bath. This interval was constant in any given assay and was usually 5 min.; with some uteri a longer interval was needed to permit the contractions from the preceding dose to subside. The complete protocol of a typical assay is shown in Table I.

TABLE I.—PROTOCOL OF TYPICAL ERGONOVINE ASSAY

Dose Number	Dose in Cc.		Latent Period in Minutes and Seconds	
	Standard	Unknown	Standard	Unknown
1	1.0	...	5 min. 30 sec.	.....
2	1.0	...	3 min. 26 sec.	.....
3	0.8	...	3 min. 18 sec.	.....
4	...	0.8	.....	2 min. 31 sec.
5	0.8	...	2 min. 10 sec.	.....
6	...	0.9	.....	1 min. 57 sec.
7	0.8	...	1 min. 58 sec.	.....
8	...	0.7	.....	2 min. 43 sec.
9	0.8	...	1 min. 59 sec.	.....
10	...	1.0	.....	2 min. 3 sec.
11	0.8	...	2 min. 42 sec.	.....
12	...	0.8	.....	3 min. 1 sec.
13	0.8	...	2 min. 54 sec.	.....
14	...	0.9	.....	3 min. 32 sec.
15	0.8	...	3 min. 27 sec.	.....
16	...	1.0	.....	2 min. 40 sec.
17	0.8	...	4 min. 16 min.	.....

RESULTS

Calculation.—In interpreting the data it is advantageous first to express the figures for the doses and the latent periods as logarithms. The latent period for a constant dose of the standard varies in a systematic manner throughout the assay. Therefore, more accurate results are obtained if the log-latent period for a given dose of the unknown is compared to the log-latent period which the standard would be expected to give at that time, instead of to the average latent period of the standard for the whole assay. This expected value is most easily obtained by averaging the log-latent period of the standard immediately preceding the given dose of the unknown and that of the standard immediately following it. The values of Y, in Table II represent such averages. Each value for the unknown is next subtracted from the corresponding value of the standard, the difference being designated X in the case of the log-dose, and Y in the case of the log-latent period. These operations are shown in Table II. The remaining computation consists of fitting a straight line to the regression of Y on X, finding the value of X on this line corresponding to a Y-value of 0, and determining the standard error of this value of X. These calculations are shown step by step in Table III.

TABLE II.—ANALYSIS OF DATA IN TABLE I

Dose Number	Log-Dose: Standard, X_s	Log-Dose: Unknown, X_u	Log-Latent Period: Standard, Observed	Log-Latent Period: Standard, Interpolated, Y_s	Log-Latent Period: Unknown, Y_u	X $(X_s - X_u)$	Y $(Y_s - Y_u)$
3	9.903–10	.....	0.519	...	...	.....	.....
4	.....	9.903–10	...	0.428	0.401	0.000	0.027
5	9.903–10	.....	0.336	...	...	.....	.....
6	.....	9.954–10	...	0.315	0.290	−0.051	0.025
7	9.903–10	.....	0.294	...	...	.....	.....
8	.....	9.845–10	...	0.296	0.434	0.058	−0.138
9	9.903–10	.....	0.297	...	...	.....	.....
10	.....	0.000	...	0.364	0.312	−0.097	0.052
11	9.903–10	.....	0.431	...	...	.....	.....
12	.....	9.903–10	...	0.446	0.479	0.000	−0.033
13	9.903–10	.....	0.462	...	...	.....	.....
14	.....	9.954–10	...	0.500	0.548	−0.051	−0.048
15	9.903–10	.....	0.538	...	...	.....	.....
16	.....	0.000	...	0.584	0.426	−0.097	0.158
17	9.903–10	.....	0.630	...	...	.....	.....

The values obtained when transformed from logarithms into ordinary numbers give the estimated potency and its standard error, 93.5 ± 3.6% in this case. This is in satisfactory agreement with the true potency of 90% to which this unknown had been made by dilution of the standard solution.

Experimental Results.—Most of the assays in which this method has been used were done as a biologic check on solutions prepared for the colorimetric analysis of ergonovine in ergot, the results of which will be reported later (7). In order to illustrate the precision obtainable with this method 10 assays were performed on solutions of ergonovine of various strengths. The true potency of these solutions was unknown to the assayist until after the computation of the results. These are shown in Table IV. It will be noted that the maximum per cent error in this series is 9.0 and the average per cent error 3.8. The departures of "Potency Found" from "True Potency" are of the extent that would be expected from the standard errors, indicating that the latter is a good measure of reliability of an assay.

Effect of Contaminants.—In view of the possibility that traces of the ergotoxine-like alkaloids might occur in certain of the solutions to be tested it was considered desirable to determine what effects the presence of various amounts of added ergotoxine would have on the apparent potency of ergonovine solutions. Eleven such assays were performed with concentrations of ergotoxine ethanesulfonate ranging between 0.0001 mg. and 0.002 mg. per cc. in the ergonovine solutions tested. With each expressed as the free base, the ratio of ergonovine to ergotoxine was from 237:1 to 12:1. Within these limits

TABLE III.—ANALYSIS OF DATA IN TABLE I

Parameter	Formula	Value
N	Number of doses of unknown	7
$S(X)$	Sum of X	−0.238
$S(X^2)$	Sum of X^2	0.027384
$S(Y)$	Sum of Y	0.043
$S(Y^2)$	Sum of Y^2	0.051459
$S(XY)$	Sum of XY	−0.027201
$\bar{x}$	$\frac{S(X)}{N}$	−0.034
$\bar{y}$	$\frac{S(Y)}{N}$	0.00614
$[x^2]$	$S(X^2) - \bar{x}S(X)$	0.019292
$[y^2]$	$S(Y^2) - \bar{y}S(Y)$	0.0511950
$[xy]$	$S(XY) - \bar{x}S(Y)$	−0.025739
b	$\frac{[xy]}{[x^2]}$	−1.3342
M	$\bar{x} - \frac{\bar{y}}{b}$	−0.0294 = 9.9706 − 10
Potency in per cent	100 (Antilog. M)	93.46%
Reduced $[y^2]$	$[y^2] - b[xy]$	0.016854
s^2	$\frac{\text{Reduced } [y^2]}{N-2}$	0.0033708
$V(X)$	$\frac{s^2}{b^2}\left\{\frac{\bar{y}^2}{b[xy]} + \frac{1}{N}\right\}$	0.0002726
s_M	$\sqrt{V(X)}$	0.01651
Standard error of potency	$2.303 s_M (100)$(Antilog. M)	3.55%

TABLE IV.—RESULTS OF ASSAYS OF "UNKNOWN" SOLUTIONS OF ERGONOVINE

Date	Number of Doses of Unknown	True Potency	Potency Found	Standard Error	Per Cent Error[a]
7-11-41	3	80	83	3.0	+3.8
7-11-41	5	125	118	4.2	−6.4
7-15-42	4	72	72	1.1	0.0
4-9-42	8	99	101	2.5	+2.0
5-10-42	12	100	91	4.2	−9.0
8-3-42	11	58	58	1.2	0.0
8-27-42	4	76	70	2.1	−7.9
8-27-42	9	76	74	1.4	−2.6
8-28-42	7	90	93	3.6	+3.3
10-5-42	7	114	111	3.9	−2.6

[a] Average per cent error = 3.8.

ergotoxine frequently caused a progressive increase in the latent period, but this action was sufficiently gradual and cumulative that the response of the standard and unknown were about equally affected and under the present experimental design little disturbance was caused in the estimate of potency. The latent period often became so excessive that it was necessary to discard the uterine segment after as few as 4 doses of the unknown solution. In the 11 assays the "Potency Found" ranged from 91% to 104% of the "True Potency," the average being 97%. In only one case (ergonovine to ergotoxine ratio of 24:1) did the ergonovine content as found by assay differ significantly ($P = 0.03$) from that actually present. In this instance the solution assayed 92% of its true value. Swanson, *et al* (8) have shown almost complete abolition of response of the isolated rabbit uterus to ergonovine after a 0.0002-mg. dose of ergotoxine, but the duration of exposure appears to have been longer than that used in the present assays.

The addition of 0.01% tartaric acid to solutions of ergonovine had no effect on their apparent potency. Ammonium tartrate and ammonium acetate at concentrations of 0.25% each increased the potency of ergonovine solutions as measured by the latent period. In the case of ammonium acetate the increase amounted to 10% ($P < 0.001$). Ergometrinine when added in equimolecular proportions to a solution of ergonovine increased the apparent potency by 18% ($P < 0.001$). At an ergonovine to ergometrinine ratio of 5:1 no such potentiation was observed. Ergometrinine alone showed no activity in doses 40 times that of the ergonovine standard.

Discussion.—Much of the accuracy of this method derives from the fact that all the information in an assay is utilized in arriving at the estimate of the potency of the unknown solution. This is in contrast to the type of assay in which an attempt is made to match the responses of the standard and the unknown, and where only doses which produce essentially equivalent responses are used to estimate the potency. From an examination of the formula for $V(X)$ in Table III it is apparent that in any given assay the error will be reduced by increasing N, the number of doses of the unknown, and by making $\bar{y}$ as small as possible. For practical purposes the latter is accomplished by selecting doses of the unknown that produce contractions with latent periods which are alternately longer and shorter than those of the standard. In computing the result an additional reduction of the error, s_M, is attained if the Y_s values are taken from a 2nd or 3rd degree equation relating the observed log–latent period of the standard to the dose number, instead of by simple linear interpolation (example in Table II). The gain is slight, however, and does not appear to justify the additional labor involved.

SUMMARY AND CONCLUSIONS

1. A method for the bioassay of comparatively pure solutions of ergonovine on the isolated rabbit uterus is described.

2. The error as determined both by the internal evidence in each assay and by the results from the assay of "unknown" solutions appears smaller than that obtained with previously reported methods.

3. Ergotoxine and ergometrinine in moderate amounts do not interfere seriously with the assay.

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Methalose Gauze and Powder for First Aid Treatment*

By Dave Brady, Robert Bauer and Fredrick F. Yonkman

Considerable interest has been directed toward obtaining better agents and methods for the treatment of burns, wounds, varicose ulcers, etc., especially so since it has long been known that tannic acid, silver nitrate and other similar agents present an undesirable feature by way of necrotizing viable cells within the injured area. This lethal action results from the precipitation of surface proteins, an action desirable for protection but of disadvantage in delaying healing.

The new preparations which are results of developments in our laboratory over the last 2 years (1, 2, 3, 4) have simplicity of compounding and of application as well as pain-relieving qualities. They contain alkyl cellulose derivatives which serve as a base for inclusion of other ingredients.

The first preparation is a new elastic type of gauze pressure dressing which contains 1% each of sulfanilamide and sulfathiazole dissolved in 5% to 20% of propylene glycol. No doubt other innocuous glycols such as butylene glycol could also be used. The glycol solution is added to a 5% aqueous solution of alkyl cellulose and the resulting liquid is sprayed or calendered over a loose, large mesh gauze. The glycols "plasticize" the cellulose and the final product is a rather durable, flexible, elastic gauze which can be applied to most injured areas. The inclusion of mineral or castor oil, 2% can be employed as an additional "plasticizer," thus enhancing the elastic qualities of the gauze film. Rolls or small sections of this medicated preparation can be sterilized by autoclaving.

We have also made films comparable to those reported recently by Pickrell (5) but found them not only too brittle, but also guilty of releasing free ammonia when autoclaved. They contained sulfanilamide, triethanolamine and methyl cellulose but no sorbitol. Our methalose gauze, because of its flexibility, adheres readily to the burned or injured area, thus tending to prevent further loss of fluid and plasma proteins. Areas of varying contour such as the breast, neck and face can be covered with smaller pieces of the moistened gauze, one overlying parts of another until the entire area is protected.

The sulfonamides are utilized as antiinfective agents. Controlled use of sulfonamides is thus realized by this method and because of the elasticity of the preparation a pressure type dressing is available in this medicated form. The viable skin cells in the traumatized area are not damaged by this preparation as they are by many commonly employed agents. Earlier and better growth of the epithelium is thus promoted, resulting in lessened indication for skin grafting in some cases. The gauze can be removed at any time by soaking with water or saline solution if wound inspection is desired and new gauze then used as a replacement. However, as long as the wound is clean and noninfected, retention of the original dressing may be desirable until complete healing occurs, as emphasized by Gurd and co-workers (6).

Recent experiments include the addition of dried plasma or of thrombin to the inner face of the gauze and of a flexible water-impervious and washable coating of ethyl cellulose over the outside of the preparation. The latter permits greater mobility on the part of the patient while the former assists in further covering the wound with a protective coating. (Fig. 1.)

The second preparation is a sulfalose or methalose powder consisting of water-soluble alkyl cellulose, 95%, sulfathiazole, 2%, sulfadiazine or sulfanilamide, 2%, and 1% eucupin dihydrochloride or other local anesthetics. Dried plasma or thrombin can also be added to this powder as is the case in the gauze film. These dried ingredients are thoroughly mixed and are best

* Received January 4, 1943, from the Department of Pharmacology, Wayne University, Detroit, Mich.

Fig. 1.—Methalose gauze 72 hours after application. Hands were washed 14 times with warm water and soap during this period. Bandages remained intact and in original positions.

applied from a larger, shaker type can such as a restaurant kitchen salt shaker.

The nonirritating, soothing and healing-promoting properties of these water-soluble, medicated preparations are their special virtues. These properties are gained without astringent precipitants or the use of a fatty or oily base.

This abbreviated preliminary report is presented with the hope that early extensive application of these data may be made by other investigators.

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Book Reviews

Drug and Cosmetics Review 1942–43. Drug and Cosmetics Industry, New York, N. Y. 8 1/2 x 11. Price, $3.00.

This is a convenient directory as well as a practical formulary and informative source of selected subjects collected from the Drug and Cosmetic Industry and other literature for the industry of drugs and cosmetics. It contains approximately 650 pages. The directory portion is in three separate sections on different colored paper for quick reference. The three sections consist of packaging and service directory, machinery and equipment directory and raw materials directory.

In the formulating section these subjects are discussed: acne, aluminum hydroxide, antiacid, anthemintics, burn therapy, beauty masks (also formulas), coughing and expectorant, dental parasiticides, enteric coatings (also formulas), foot preparations (also formulas), foundations for make-up (3 formulas), hair dyes (also describes ingredients), hand lotion manufacture, insect bites, insect repellents, ointment vehicles (no formulas) pruritis, perfuming cosmetics (no formulas), permanent wave solutions, shaving (2 formulas mostly discussion), skin protectives, local use of sulfonamides (1 formula), toothpaste preparation and deodorants, and storing essential oils. Most of these articles contain formulas, although some are devoted entirely to a review of the subject and many articles are accompanied by a bibliography. Besides all of these formulas there are several hundreds of others on creams of all kinds, face powders, shampoos, astringent lotions, bath salts, hair dressings and other cosmetic preparations.

This book has been compiled at a time when the availability of materials is uncertain. The advertisers have been urged to retain their listings as of a normal period so that the buyer will find greater use of the book after the period of uncertainty. Price movements of about 1000 raw chemicals over a ten-year period up to and including the year 1941 are given in the concluding pages.

This book is an asset to the buyers for drug and cosmetic manufacturers and will be found valuable to their compounding departments.—E. C. BEELER

Organic Chemistry, An Advanced Treatise, Edited by HENRY GILMAN, Iowa State College. Second edition. John Wiley and Sons, Inc., New York,

N. Y. 1943. Two Volumes. Vol. I, ix + 1077 pp.; Vol. II, ix + 906 pp., 15 x 23 cm. Price, $7.50 per volume.

The appearance of the second edition of this outstanding work marks an important milestone in the development of the literature of organic chemistry. Covering most of the important phases of the science, the work of experts writing in the fields of their particular interests, and the whole admirably integrated, this book is second to none of its kind.

Volume I deals with the more general and fundamental aspects of organic chemistry while, for convenience in revision and expansion, the rapidly developing fields of natural products, relationship between physical properties and chemical constitution, valence, and resonance have been grouped in the second volume. Consideration of the table of contents will indicate the scope and importance of the material and the capabilities of the several authors. Volume I includes the following chapters: The Reactions of Aliphatic Hydrocarbons, by Gustav Egloff, Universal Oil Products Company; Alicylic Compounds and the Theory of Strain, by Reynold C. Fuson, University of Illinois; Theory of the Structure and Reactions of Aromatic Compounds, by Louis F. Fieser, Harvard University; Stereoisomerism, by Ralph L. Shriner, Indiana University, and Roger Adams and C. S. Marvel, University of Illinois; Organometallic Compounds, by Henry Gilman, Iowa State College; Free Radicals, by Werner E. Bachmann, University of Michigan; Unsaturation and Conjugation, by C. F. H. Allen, Eastman Kodak Company, and A. H. Blatt, Queens College; Synthetic Polymers, by C. S. Marvel and E. C. Horning, University of Illinois; Catalytic Hydrogenation and Hydrogenolysis, by Homer Adkins, University of Wisconsin, and Ralph L. Shriner; Organic Sulfur Compounds, by Ralph Connor, University of Pennsylvania; Aliphatic Fluorides, by Albert L. Henne, Ohio State University; Molecular Rearrangements, by Everett S. Wallis, Princeton University; Comparison of Chemical Reactivity, by Homer Adkins. The chapters on reactions of aliphatic hydrocarbons, synthetic polymers, catalytic hydrogenation and hydrogenolysis, organic sulfur compounds, and aliphatic fluorides are new to this edition.

The following chapters constitute Volume II: Natural Amino Acids, by H. T. Clarke, Columbia University; Alkaloids, by Lyndon Small, National Institute of Health; The Chemistry of the Porphyrins, by Alsoph H. Corwin, Johns Hopkins University; Chlorophyll, by Catherine C. Steele, Huntingdon Valley, Pennsylvania; the Anthocyanins and the Flavones, by Karl Paul Link, University of Wisconsin; the Steroids, by William H. Strain, Eastman Kodak Company, and School of Medicine and Dentistry, the University of Rochester; Carbohydrates I, by Melville L. Wolfrom, Ohio State University; Carbohydrates II, by Albert L. Raymond, G. D. Searle and Co.; Carbohydrates III—Cellulose, by Emil Heuser, Institute of Paper Chemistry; Constitution and Physical Properties of Organic Compounds, by J. A. Leermakers and A. Weissberger, Eastman Kodak Company; The Redistribution Reaction, by George Calingaert and Harold A. Beatty, Ethyl Corporation Research Laboratories; Modern Electronic Concepts of Valence, by John R. Johnson, Cornell University; The Significance of Resonance to the Nature of the Chemical Bond and the Structure of Molecules, by Linus Pauling, California Institute of Technology. New chapters in this volume are those dealing with the chemistry of the porphyrins, chlorophyll, and the redistribution reaction.

Numerous cross references and individual tables of contents for each chapter, as well as a comprehensive subject index which is repeated in each of the volumes, increase the accessibility of the information. References to the original literature are necessarily restricted but are mostly to recent publications or to those which provide historical backgrounds. In some instances the literature has been reviewed up to September, 1942, and some of the work described was previously unpublished. It is pleasing to note that it is the intent of the editorial board to keep the book abreast of developments in the field of organic chemistry since "it can but serve the purpose of the moment and provide a point of departure for unceasing revision."

The book is intended for instruction in organic chemistry at the graduate level and it is admirably suited to this purpose. However, its utility extends far beyond such a limited scope. As a source of information for the teacher and investigator it is perhaps unsurpassed by any similar book. The wealth of material concerning natural products as well as the more general aspects of organic chemistry render it an invaluable aid to the teacher of advanced pharmaceutical chemistry.—E. L. CATALINE.